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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,248	03/29/2004	Alex J. Harvey	AVI-027N	2313
26739	7590	08/03/2006	EXAMINER	
AVIGENICS, INC. 111 RIVERBEND ROAD ATHENS, GA 30605			WILSON, MICHAEL C	
			ART UNIT	PAPER NUMBER
			1632	
DATE MAILED: 08/03/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/812,248

Applicant(s)

HARVEY ET AL.

Examiner

Michael C. Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 June 2006.
2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 33-42 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-10 and 33-42 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12-20-04.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-10, in the reply filed on 6-8-06 is acknowledged.

Claims 11-32 have been canceled. Claims 33-42 have been added. Claims 1-10 and 33-42 are pending and under consideration in the instant office action.

Specification

The application number on pg 19, line 29, will have to be updated upon being allowed or abandoned.

The temperature on pg 35, line 16, has an error.

The sentence at the end of the first paragraph on pg 48 does not have a period and is incomplete.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 33-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for integrating a transgene into avian blastodermal cells by electroporating the transgene into the avian blastodermal cells, does not reasonably provide enablement for integrating a transgene into an avian totipotent cell by electroporating the transgene into avian blastodermal cells. The specification does not enable any person skilled in the art to which it pertains, or with

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which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to producing an integrated transgene in an avian cell comprising introducing a nucleic acid sequence comprising a non-lethal marker gene into an avian cell by electroporating; and allowing the cell to undergo a cellular division; thereby producing an integrated transgene in an avian cell. Claim 1 encompasses stably integrating a transgene into totipotent avian cells.

Claim 33 is drawn to producing an integrated transgene in a totipotent avian cell comprising introducing a nucleic acid sequence comprising a non-lethal marker gene into an avian cell by electroporating; and allowing the cell to undergo a cellular division; thereby producing an integrated transgene in a totipotent avian cell.

Naito (J. Poultry Sci., Oct. 2002, Vol. 39, pg 292-301) electroporated blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP and put the cells in culture to undergo cellular division (pg 294, "Embryo manipulation and plasmid DNA" "Transfection of stage X blastoderms by electroporation in vivo" and "Embryo culture and detection of gene expression"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Naito taught GFP expression persisted from day 1 to day 3, which is an indicator that the transgene is stably integrated into the cells of the developing embryo (see pg 48, lines 3-15 of the instant application).

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Naito (J. Poultry Sci., Oct. 2003, Vol. 40, pg 319-323) used the method of Naito (2002) to transfect blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP. "Following the electroporation of stage X blastoderm in vivo, a total of 47 chickens were hatched and 29 chickens grew to maturity (Table 2). The introduced DNA was not detected in the sperm samples of the male chickens, and the GFP gene expression was not detected in the embryonic samples of the female chickens" (pg 321, lines 1-5). Naito concludes, "in vivo electroporation of stage X blastoderm can not be expected to integrate the introduced DNA into the chromosomes of the germline cells" (pg 322, last sentence).

Thus, the art at the time of filing did not teach how to integrate a transgene into the genome of blastodermal avian cells by electroporation.

The specification taught electroporating chicken blastodermal cells (CBC). Pg 48, lines 3-19, states:

"In order to determine whether the transgene had integrated into the chicken genome, 34 green fluorescent CBC colonies were picked up after transfection of BDCS with linearized pOVT7.4/0.875-IFN-RSV-EGFP and cultured for 96 hours (this is defined as the primary culture). These colonies were dissociated by pipeting method and cultured in a well of 24 well-plate contained STOs and using BDC-CEE medium (see Methods section). After three days culture about 50% of the resulting colonies exhibited green fluorescence in whole colony (Figure 4 A,B)(this is defined as passage one). Others had no green fluorescence. Several undifferentiated homogenous green fluorescent colonies were picked up from the passage one culture, dissociated and cultured on STOs with BDC-CEE medium. A11 colonies exhibited homogenous green fluorescence in this and subsequent passages (Figure 4C, D, E, F). The homogenous green fluorescent colonies were continuously cultured to passage 11 on the 10 centimeter gelatin dishes and the DNA was extracted for southern blot analysis (Figure 10, lane 9). A single band of ~13 kb was detected in Bam HI digested genomic DNA by the IFN probe. With integration, a band larger than 8.5 kb would be expected. Therefore, confirmation [sic]"

It is noted that the last sentence of the paragraph indicating "confirmation" is incomplete. The specification does not provide any indication that totipotent cells of the CBC colonies have the transgene integrated as implied in claim 33. Without such guidance, it would require those of skill undue experimentation to determine how to overcome the unpredictability in the art, i.e. how to integrate a transgene into the genome of totipotent avian cells.

Wang (Stem Cells, 2006, Vol. 24, pg 1638-1645) taught the method described by applicants (electroporation of CBCs followed by culture in chick embryo extract) and explains why bands larger than 8.5 kb indicate the transgene is integrated into CBC colonies (pg 1641, col. 2, "The puromycin-resistant transgenes are integrated").

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 9, 10, 33, 35, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei (Poultry Sci., 2001, Vol. 80, pg 1671-1678).

Wei electroporated chicken blastodermal cells (CBC) with a plasmid encoding LacZ. The cells were put in culture and allowed to undergo cellular division for 24, 48 or 72 hours (pg 1672, "Isolation and electroporation of CBC"). Some of the cells inherently

have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). Any integration, including low integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Wei inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Claims 1, 3, 9, 10, 33, 35, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Etches (Poultry Sci., 1997, Vol. 76, pg 1075-1083).

Etches electroporated CBC with a plasmid encoding LacZ and put the cells in culture to undergo cellular division (pg 1080, "Transfection"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Etches teaches the absence of the LacZ in tissues from chimeras made with electroporated cells indicates that it is stably integrated into the genome of CBCs "only rarely" (pg 1080, column 2, lines 10-13). Any integration,

including low or rare integration, meets the limitation of “producing an integrated transgene” or “stably integrated” as claimed. Without evidence to the contrary, the method of Etches inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase “producing an integrated transgene in a totipotent avian cell” in the preamble is an intended use and does not have to occur and 2) the phrase “thereby producing an integrated transgene in a totipotent avian cell” indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Claims 1, 3-6, 9, 10, 33, 35-38, 41 and 42 are rejected under 35 U.S.C. 102(a) as being anticipated by Naito (J. Poultry Sci., Oct. 2002, Vol. 39, pg 292-301).

Naito electroporated blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP and put the cells in culture to undergo cellular division (pg 294, “Embryo manipulation and plasmid DNA” “Transfection of stage X blastoderms by electroporation in vivo” and “Embryo culture and detection of gene expression”). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Naito taught GFP expression persisted from day 1 to day 3, which is an indicator that the transgene is stably integrated into the cells of the developing embryo (see instant application on pg 48, lines 3-15). Any integration,

including low or rare integration, meets the limitation of “producing an integrated transgene” or “stably integrated” as claimed. Without evidence to the contrary, the method of Naito inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase “producing an integrated transgene in a totipotent avian cell” in the preamble is an intended use and does not have to occur and 2) the phrase “thereby producing an integrated transgene in a totipotent avian cell” indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9, 10, 33-35, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei (Poultry Sci., 2001, Vol. 80, pg 1671-1678) in view of Nicolas-Bolnet (Poultry Sci., 1995, Vol. 74, pg 1102-1116).

Wei electroporated chicken blastodermal cells (CBC) with a plasmid encoding LacZ. The cells were put in culture and allowed to undergo cellular division for 24, 48 or 72 hours (pg 1672, "Isolation and electroporation of CBC"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). Any integration, including low integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Wei inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid

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into a totipotent avian cell because 1) the phrase “producing an integrated transgene in a totipotent avian cell” in the preamble is an intended use and does not have to occur and 2) the phrase “thereby producing an integrated transgene in a totipotent avian cell” indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell. Wei did not allow the cells to undergo division in the presence of chick embryo extract (CEE).

However, Nicolas-Bolnet taught CEE increased proliferation of chicken pluripotent cells (pg 1107, “Chick embryo extract or fetal bovine serum-free culture”).

Thus, it would have been obvious to those skilled in the art at the time the invention was made to electroporate CBCs as taught by Wei and allow the cells to undergo cell division in the presence of CEE as taught by Nicolas-Bolnet. One of ordinary skill would have been motivated to add CEE to the culture medium to provide growth factors available to blastodermal cells in an embryo and to increase proliferation of blastodermal cells as taught by Nicolas-Bolnet.

Thus, Applicants’ claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 9, 10, 33-35, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etches (Poultry Sci., 1997, Vol. 76, pg 1075-1083) in view of Nicolas-Bolnet (Poultry Sci., 1995, Vol. 74, pg 1102-1116).

Etches electroporated CBC with a plasmid encoding LacZ and put the cells in culture to undergo cellular division (pg 1080, “Transfection”). Some of the cells

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inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Etches teaches the absence of the LacZ in tissues from chimeras made with electroporated cells indicates that it is stably integrated into the genome of CBCs "only rarely" (pg 1080, column 2, lines 10-13). Any integration, including low or rare integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Etches inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell. Etches did not allow the cells to undergo cellular division in the presence of CEE.

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Thus, it would have been obvious to those skilled in the art at the time the invention was made to electroporate CBCs as taught by Etches and allow the cells to undergo cell division in the presence of CEE as taught by Nicolas-Bolnet. One of

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ordinary skill would have been motivated to add CEE to the culture medium to provide growth factors available to blastodermal cells in an embryo and to increase proliferation of blastodermal cells as taught by Nicolas-Bolnet.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefore..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 5 and 37 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 4 and 36. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The phrase "wherein the marker gene is a fluorescent expression marker" is substantially the same as "wherein the marker is a fluorescent protein expression marker."

Conclusion

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The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Wong (1999, Transgenic Animals in Agriculture, ed J.D. Murray, CABI Publishing, pg 117-129)

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER